MEDICAL REVIEWER'S REPORT

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PLA 97-0006
MEDICAL REVIEWER'S REPORT

COVER SHEET

PRODUCT: Epoetin alfa [PROCRIT and EPOGEN]. There are no changes in the products in connection with this supplement.

SPONSOR: AMGEN INC., 1840 DeHavilland Drive, Thousand Oaks, CA 91320-1789

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REVIEW SCHEDULE/MILESTONES/TIMELINES:
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Committee Assignment: January 17,1997
Filing action by: March 4, 1997: Committee recommended that PLA be filed.
Mid-cycle review: April 8, 1997
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Final action : July 3, 1997
Committee recommendation that an approvable letter be sent contingent on agreement on package insert labeling: June 9,1997

ABBREVIATIONS USED:
HD is hemodialysis
PD is peritoneal dialysis
CRF is chronic renal failure
Hct is hematocrit
CRF is chronic renal failure
TX is transfusion
BIW is twice a week (drug dose); TIW is three times a week
CMH is Cochran Mantel Haenszel analysis
FSR is sponsor Final Study Report
SOE is sponsor Summary of Efficacy

The treatment arm is referred to in upper case as EPOETIN arm; the placebo arm as the CONTROL arm. The drug Epoetin alfa is referred to as Epoetin.

Reviewers comments are in *italics* or *bold italics*. Sources are indicated in parentheses /smaller font.

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ENCLOSURES

1. Sponsor's proposed revised labeling
2. Study calendars
3. Sponsor's tabulation of Severe, Life threatening and Fatal AE and Serious AE
4. Verbatim listing of terms for Preferred Term myalgia

PART I-INTRODUCTION

PRODUCT: Epoetin alfa [PROCRIT and EPOGEN]. There are no product changes in connection with this supplement.

SPONSOR: AMGEN Incorp.

INDICATIONS: The data/information provided will support changes in the labeling of Epoetin alfa for correction of anemia and reduction of blood transfusion requirements in the following clinical situations:

1. *pediatric* chronic renal disease (CRF) patients on dialysis
2. *pediatric* CRF patients not on dialysis
3. *pediatric* cancer patients who have received chemotherapy
4. HIV-infected *pediatric* patients with anemia secondary to zidovudine-treatment

BACKGROUND AND RATIONALE: Epoietin alfa was approved for correction of anemia in adults with chronic renal failure (CRF) in 1989 on the basis of *its ability to increase hematocrit/hemoglobin to a target level and maintain the increase over time as well as decreased need for red blood cell transfusion support.* Licensure was supported by data indicating improvements in quality of life. Labeling for Epoetin alfa specifically precludes its use for correction of severe anemia or use in emergency situations. Since 1989, numerous reports of off-label use of erythropoietin in children have suggested Epoetin has comparable activity and safety to that in adults. The estimated number of new cases of chronic renal disease in children is one per 100,000 population /year (U.S.) or an estimated 24,000 new cases a year.

It has been observed that the anemia associated with CRF in the pediatric age group is more severe than in adults having the same degree of renal disease (referenced to Muller-Weifel, DE, Scigallla , P., Contrib Nephrol. 1988;66:71-84). The anemia and the need for repeated blood transfusions is a factor in the children's physical impairments and poses medical problems. Frequent blood transfusions may result in serious indirect complications. These include: a) iron overload; b) febrile and hemolytic reactions to leukagglutinins; c) cytotoxic HLA antibodies which could compromise and limit later renal transplants. In addition transfusions pose risks in transmission of infectious agents including HIV, CMV, hepatitis C.

It has been speculated that there are differences in response to erythropoietin between children receiving different modes of dialysis. In a review of pediatric renal failure, endogenous Erythropoietin concentrations were 24.6± 2.1, and 41.6±5.6 and hematocrits were 22.2±, and 25.2± 0.8, in hemodialysis and peritoneal dialysis patients respectively (referenced to Muller-Weifel, DE, Scigallla , P. Contrib Nephrol. 1988;66:71-84). These data were in children who had not received exogenous Epoetin therapy.

The present supplemental application supports changes in Epoetin alfa labeling for pediatric use. The changes in labeling are supported by 4 clinical trials at nineteen sites, by published medical literature and by analyses of post marketing safety data (see Sources of Data/Information below).

SOURCES OF DATA/INFORMATION:

Sponsor submitted data: The major source of data was the initial sponsor application of 45 volumes submitted December 31, 1996 , log # L97000070. An outline of its organization is shown in the table labeled , ORGANIZATION OF THE APPLICATION BY SECTION AND VOLUME. Data tables/figures were available from a number of sources which included the Final Study Report (FSR) [Section 10]; the Summary of Efficacy (SOE) [Section 3.3 and attachments] and the Integrated Safety Summary found in Section 3.4 and attachments -volumes 1 and 2. There are minor discrepancies between the SOE and FSR attributable to the fact that additional information became available only after the FSR had been completed. The SOE and Integrated Safety Summary served as the main but not exclusive source for the Reviewer report .

Additional material submitted by sponsor at CBER request:

- Log number # L97004881 , March 17, 1997, one volume, sponsor proposed revisions in package insert on computer discs
- Log number L97005974, April 1, 1997, one volume, information on completeness of computer search literature review
- Log number L97006095, April 4, 1997, one volume, data on patient- i) list of verbatim terms reported as " myalgia" (Preferred term) ; ii) years of patient exposure to Epoetin alfa

STUDIES AND OTHER REVIEWED MATERIAL: Data from four prospective sponsor-conducted clinical trials support pediatric licensure for the first indication, that is, correction of anemia in children with CRF on dialysis. The first two of these trials, EPO-8702 and EPO-8905 showed safety and activity in small, pilot studies (n=5 and 10 subjects). They were followed by EPO-9002, a larger (n=113), double blinded, placebo-controlled study in pediatric CRF patients undergoing dialysis. At termination of EPO-9002, 74 of 113 subjects patients were entered into a long term maintenance study, EPO- 9118. Relevant data on subject number, dialysis type, experimental design and study duration are shown in table below.

A literature review supports pediatric licensure for the first indication (source-section 3.5, vol. 3).

A literature review supports pediatric licensure for the 2nd, 3rd , 4th indications (source-section 3.6, vol. 3).

Additional safety data from 21 pediatric subjects is provided by [redacted] (source-vol. 44, appendix 3.6C)

Additional reports of postmarketing AE in pediatric patients is provided from both AMGEN and [redacted] (source- vol. 44, appendix 3.6D).

PROPOSED LABELING: The new labeling submitted by sponsor is found in enclosure 1. CBER will revise the above further. Special concern to CBER reviewers are :

1. Page volume 1/9 makes the statement that , " The pharmokinetic profile of EPOGEN/PROCRIT in children and adolescents appears to be similar to that of adults". Pharm./Tox. review by Dr. Green will evaluate this statement.

[redacted]

FOUR SPONSOR CONDUCTED STUDIES

EPO-8702: Treatment of Patients Undergoing Continuous Ambulatory Dialysis /Continuous Cycling Peritoneal Dialysis with Recombinant Human Erythropoietin by Subcutaneous Administration (n=5).

EPO-8905: A, Double blind, Placebo-controlled Study of Recombinant Human Erythropoietin in Pediatric Dialysis Patients (n=10).

EPO-9002: A Phase 3, Double-blind, Placebo-controlled study of EPOGEN® (Epoetin alfa) in Pediatric Dialysis Patients (n=113).

EPO-9118: Long-term Maintenance Treatment of Chronic Pediatric Dialysis Patients with Recombinant Human Erythropoietin (Epoetin alfa) (EPOGEN®) (n= 74).

Study	Age range years	Mean Age(±S.D.) years	Dialysis Mode	Duration of Study**	Study started	Study ended	Experimental Design
EPO-8702 n=5	12-19	15.8±3.5	PD	12 weeks	8/26/87	6/7/89	Single arm, pilot study
EPO-8905 n=10	7-18	13.6±4.1	HD	up to 2 years	11/6/89	1/22/92	Two arm, placebo controlled, randomized
EPO-9002 n=113	0.2-17.9	11.7±5.2	HD/PD	Epoetin arm 36wk; Control 48 wk**	11/21/90	8/31/93	Two arm, placebo controlled, double blinded, randomized
EPO-9118 n=74	1.1-19.0	13.4±4.8	HD/PD	12 months**	3/1/3/92	12/29/93	Single arm of subjects from 9002 on maintenance
all studies n=128*	0.2-19.0	12.5±5.0					

* 74 patients crossed over from EPO-9002 to EPO- 9118 ** Both studies were administratively terminated early and not all subjects completed the full experimental program

PD is peritoneal dialysis; HD is hemodialysis

ORGANIZATION OF THE APPLICATION BY SECTION AND VOLUME

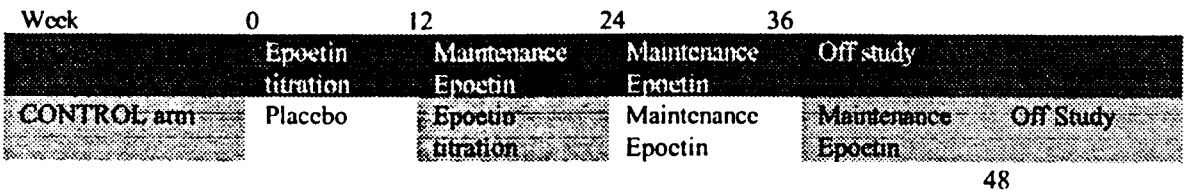
VOLUME	DESCRIPTION	SECTION
1	General information, rationale, and introduction to study	1 & 2
	Study Report of efficacy in pediatric CRF patients on dialysis plus Attachments (supporting tables, figures and lists)	3.3
1&2	Study Report of integrated safety data including postmarketing reports, attachments , supporting tables, figures & lists	3.4
3	Literature review supporting indication for pediatric patients on dialysis- 61 papers	3.5
	Literature review supporting indication for correction of anemia associated with ziduvudine use, cancer and in CRF patients not on dialysis - 42 papers	3.6
	Antibodies to erythropoeitin in patient sera	4.0
	Pharmocokinetics for pediatric CRF patients on dialysis	5.0
3	List references for sections 3.4 and 3.6 (n=103)	9.0
4 and 5	Clinical Study Report for EPO- 9002, plus tables and figures	10.1
6	Clinical Study Report for EPO- 9002	
	Study protocol starting 8/29/90, amended & dated 3/23/93	Appendix A.1
	Case Report forms	Appendix A.2
	Serious AE reports , CRFs and autopsy report patient 0104	Appendix A.3
	Various tables and figures	Appendix B.1/2
7 thru 25	Clinical Study Report for EPO- 9002 incl. statistical analyses	Various appendices
15	List of AE patient by patient	
26	Clinical Study Report for EPO- 9002	
	By patient plot of weekly dose, hct, and AE over time	Appendix F.1
	By patient plot of systolic & diastolic B.P. over time	Appendix F.2
	By patient plot of Tf, ferritin, & Fe supplement over time	Appendix F.3
27-28	Clinical Study Report for EPO- 9002-Investigator Comment Log	
29	Clinical Study Report for EPO- 9002- Nutrition studies	Attachments 1-4
30	Clinical Study Report for EPO- 9002-Cognitive function and Bone Age	
31-38	Clinical Study Report for EPO-9118	
39-41	Clinical Study Report for EPO-8905	
42	Clinical Study Report for EPO-8702	
42	Data listings for pediatric CRF patients on dialysis	appendix 3-1
42	Patient ID codes for pediatric CRF patients on dialysis	appendix 3-2
42	Postmarketing experience for pediatric CRF patients on dialysis	appendix 3-5
42	Sponsor-prepared abstracts of literature for pediatric CRF patients on dialysis	appendix 3-6a
43	Full articles/abstracts supporting pediatric CRF patients on dialysis	appendix 3-6b
44	Post marketing experience listings and CIOMS forms	appendix 3-6d
45	Articles supporting indication for CRF patients not on dialysis/ Zidovudine, cancer	appendix 3-6c

PART IIa- STUDY EPO -9002

1. STUDY DESIGN

Overview: Study EPO-9002 is the major study supporting use of Epoetin in pediatric patients with chronic renal disease. It was a 113 patient, multi-institutional, two arm study (EPOETIN arm and CONTROL arm) with 16 listed sites/ Principal Investigators.

Experimental design: Following enrollment, patients were randomized in approximately equal numbers to each arm. The first 12 week period was double blinded ; after that point the remainder of the study was open label. Stratification was by site and within the sites by method of dialysis (hemodialysis vs. peritoneal dialysis) and by ages 0-<5, 5-<15, 15-<18 creating six stratification cohorts in each center.



The study arms were divided into 12 week or multiples of 12 week phases- as outlined in the above schematic. The first phase was weeks 1- 12 weeks of the study in both arms and was referred to as the double-blind phase. During the double blind phase EPOETIN arm subjects were titrated with Epoetin while the CONTROL arm subjects received a placebo. At end of week 12, the CONTROL arm was crossed over to Epoetin titration using the same dosing rules applied to the EPOETIN arm, while EPOETIN arm patients started a Epoetin maintenance phase to last 24 weeks. At week 36 the EPOETIN arm subjects went off-study. The CONTROL arm completed Epoetin titration at end of week 24 and began the 24 week maintenance phase. At week 48 the CONTROL arm subjects went off study.

Planned analyses: Titration and maintenance phases were non- concurrent (see schematic above) to permit a comparison for treatment effect of Epoetin titration vs. placebo treatment during the first 12 weeks. The use of crossover to Epoetin titration and the non-concurrent maintenance phases insured that all 113 patients in both arms received full titration and maintenance courses of Epoetin and permitted analysis of all patients for responses to Epoetin therapy. Four primary endpoints which were analyzed at three critical timepoints..

Primary efficacy endpoints:-comparison Epoetin vs. placebo arms during double blind phase

- for fraction of subjects in each arm attaining target hematocrit*
- for mean hematocrit level
- for mean numbe of transfusions/patient/4 weeks of study

and for maintenance dose of Epoetin for maintenance phase of study arms

Critical efficacy timepoints:

-end of first 12 week "double blind" phase at which time the EPOETIN and CONTROL arms could be compared for treatment effect

- end of Epoetin dose titration after each group had received 12 weeks of Epoetin of Epoetin (EPOETIN arm week 12; CONTROL arm week 24)
- End of maintenance phase comparison after each group had received 24 weeks of maintenance Epoetin (EPOETIN arm week 36; CONTROL arm week 48)

* Target hematocrit was attainment of 30-36% target hematocrit or increase of 6% hematocrit points above baseline at any point during the 12 week Epoetin titration period.

Secondary endpoints included transfusion independence; Epoetin alfa dose needed to achieve target level in U/kg/week; rate of hematocrit rise in points /week; cognitive function; growth assessment and sexual development; serum ferritin, transferrin saturation; dose of supplemental iron needed; blood pressure; serum chemistry determinations, and others -see list under efficacy.

Safety endpoints included incidence of AE; laboratory chemistry and hematology abnormalities; vital signs including blood pressure.

Statistical analyses: Continuous variables with a normal distribution were analyzed by paired t tests; if the distribution was not normal a non-parametric test was used. Dichotomous data were compared using Chi Square testing or Fisher's Exact test. Stratified data analysis and comparison of fraction of patients in each arm to attain the target hct employed the Cochran-Mantel-Haenszel analysis. The majority of secondary endpoints were descriptive and were not analyzed statistically.

Power estimates made in original protocol: Estimates of the power for the four efficacy endpoints were as follows. By the end of the double blind period, 90% of EPOETIN arm patients as compared to 10% of CONTROL arm subjects would attain the target level demonstrating the treatment effect. Twelve to 16 patients per group/arm would provide a significance level of 0.01 to 0.005 and power of 0.9 to 0.99. The same numbers of patients would be adequate to show a significant difference of 6 hematocrit % points between HD EPOETIN and HD CONTROL groups at the same significance level and power. It was estimated that 20 patients per group/arm would be needed to show a difference of one transfusion /patient/month between the two study groups during the first 12 week period (0.01 significance level, power 0.9). Power calculations assumed a high dropout rate and projected that 50 patients per group/arm were needed to meet all primary endpoints.

It was anticipated that at the end of the Epoetin titration phase there would be a positive treatment effect (increase of hematocrit to target level and lessened need for transfusion) present in both arms. A greater than 2 hematocrit point difference between groups was viewed as clinically significant. With 30 patients per group, a 2 % or > difference in hematocrit could be detected at 0.01 level of significance with 90% power assuming the hematocrit at the end of 12 weeks was 27% or higher.

Limited rises in hematocrit were expected during the maintenance phase. At the end of the maintenance phase a similar treatment effect in each arm was anticipated (increase of hematocrit to target level and lessened need for transfusion). To show that the difference between arms was no greater than 3 hct points, it was estimated that 30 patients were needed (significance level of 0.01, power of 90%).

Study subjects: All subjects were children with CRF less than 18 years of age at time of study entry who were currently on either hemodialysis (HD) or peritoneal dialysis(PD). Pre-transfusion hematocrits on at least two occasions had to be less than or equal to 27%. If transferrin saturation was < than 20%, the patient received a course of parenteral iron 30 days prior to study entry. Individuals who had received prior Erythropoietin treatment or other investigational agents/drugs were excluded .

Dosing: During the double blind phase (first 12 weeks), both hemodialysis and peritoneal dialysis patients in the EPOETIN group received a dose of 150 Units/kg per week given T.I.W. Peritoneal dialysis patient received subcutaneous (SC) injections of Epoetin alfa while hemodialysis patients were given Epoetin by the intravenous route. The dose could not increased until week 16 but could be reduced before then using different adjustment strategies for HD and PD patients as follows: For HD patients, when hematocrit reached 33% or > on two consecutive measurements or the rate of rise was > than 2%/week for two weeks, the dose was lowered by 10 Units/kg maintaining the T.I.W. dose schedule- allowing 2 week intervals between dose reductions. PD patients under the same circumstances had the 50 Units/kg dose reduced to BIW and then to once a week- if necessary.

The CONTROL arm received a placebo preparation during the double blind phase which contained only the excipient 0.25% albumin in isotonic saline and sodium citrate buffered solution. The placebo solution was non-pyrogenic , sterile , clear, colorless and particle-free and identical to the vehicle used for commercial Epoetin.

During the maintenance phase the goal was to achieve a stable hematocrit between 30-36%. If the hematocrit rose above 36% the dose was reduced by 10 Units/kg in HD subjects or by elimination of one of the weekly doses in the PD patients. The dose could be increased after 16 weeks of Epoetin therapy had been completed (week 4 of maintenance phase) to bring the patient into the 30-36% hct dose range as follows: PD patients who were receiving less than T.I.W. injections would have the number of SC injections increased to T.I.W. and then the dose would be increased by 10 Units/kg. HD patients would have doses increased by 10 Units/kg . Two week intervals would be maintained between adjustments.

Monitoring: The experimental schedule and tests are listed in the study calendar -see enclosure 2. Routine studies included history and physical examination, chest ray, complete blood count and differential, serum iron level, transferrin saturation, platelet and reticulocyte determination, and clinical chemistry including coagulation studies. More specialized testing included nutrition assessment, evaluation of endocrine status, gonadal tests, bone age determinations , and cognitive function tests (see secondary efficacy endpoints). Erythropoeitin antibody determinations were performed at intervals (see calendar- enclosure 2). Safety data and data needed for various secondary endpoints including adverse events, number of transfusions of blood, number of days of hospitalization, changes in dialysis strategy and concomitant medications were recorded. Quality of life issues including growth assessment, nutritional status, thyroid function, cognitive and quality of life testing were analyzed separately using a battery of tests.

Concomitant medications were permitted at the discretion of the physician; the only exceptions were other investigational agents, and immunosuppressives/ androgens for hemodialysis patients. If during the study the patients transferrin saturation fell to < 30%, patients received oral iron supplementation at a dose 1-2 mg/kg and parenteral iron if oral supplementation failed.

Blood pressure was closely monitored. It was recommended that the dose of Epoetin alfa be decreased if the hct increase exceeded 4% in a 2 week period.

2. CONDUCT OF THE STUDY

Disposition of patients: 113 patients were randomized; 55 to the EPOETIN arm and 58 to the CONTROL arm. 102 patients completed the double blind phase of the study (11 discontinuations); 64 patients completed the full study (49 discontinuations). The major reasons for discontinuation/failure to complete full course of study were renal transplantation (n= 18) and the administrative decision to terminate the study early- in August 1993 (n=15).

During the double blind phase (first 12 weeks of study) there were 11 discontinuations; 3 in the EPOETIN arm and 8 in the CONTROL ARM. In the 3 discontinuations from the EPOETIN arm, 2 subjects were transplanted with kidneys and one died. In the CONTROL arm, one patient had intolerable AE (hypertension and siezures), one patient was non-compliant (family problems), one patient was transplanted, and four patients requested withdrawal - two so they could receive open- label Epoetin, one due to change of modality of dialysis and one due to discomfort from repeated injections. Information was not available on one subject.

The reasons for the 49 discontinuations during the maintenance phase are shown in the second table below.

There was a higher number of discontinuations among patients in the CONTROL arm. A large fraction of these were accounted for by renal transplants and patient withdrawal. The difference was consistent with a less satisfactory quality of life of CONTROL vs. the EPOETIN arms.

Phase of study	EPOETIN arm (HD, PD)	CONTROL arm (HD, PD)	totals
Double-blind			
entered	55 (24, 31)	58 (24, 34)	113
discontinued	3 (1, 2)	8 (3, 5)	11
Crossover			
entered	0	50 (21, 29)	50
discontinued	0	9 (5, 4)	9
Maintenance			
entered	52 (23, 29)	41 (16 25)	93
discontinued	13 (6, 7)	16 (5, 11)	29
completed	39 (17, 22)	25 (11, 14)	64

Reasons for withdrawal during the maintenance phase

	EPOETIN arm (HD, PD)	CONTROL arm (HD, PD)
Total discontinued by end of maintenance phase	16 (7, 9)	33 (13,20)
patient withdrew	0	5 (1, 4)
renal transplant	5 (3, 2)	13 (5, 8)
administrative decision	7 (3, 4)	8 (4, 4)
intolerable AE	0	1 (0, 1)
lost to follow up	1 (0, 1)	0
death	1 (0, 1)	0
completed < 48 wks	1 (0, 1)	1 (0, 1)
non-compliance	0	2 (1, 1)
protocol violation	1 (1 0)	0
other reasons	0	3 (2, 1)

Changes/amendments to Original protocol: There were four amendments to protocol; the first two were limited and without consequences to study. The third replaced eligibility criteria on page 7/section 4.1.3 and treatment on page 23/section 9.1.9 as follows. Entry criteria was changed to transferrin saturation (> 20%) alone rather than both transferrin saturation and serum ferritin. The same alteration in criteria was made for initiation of parenteral iron therapy. The fourth amendment changed entry criteria from < 1000 to < 2000 ANC /mm^3.

3. RESULTS - BASELINE DEMOGRAPHIC/CLINICAL FEATURES: EPOETIN and CONTROL arms and HD and PD groups had similar characteristics. Approximately one half of the patients were hypertensive and on medications for blood pressure control. Age data is given in section 5.

	HD Epoetin n=24	HD Control n=24	PD Epoetin n=31	PD Control n=34	TOTAL Epoetin n=55	TOTAL Control n=58
Sex Male	54	63	64.5	56	60	59
Female	46	38	35.5	44	40	41
Race Caucasion	38	25	35.5	41	36	35
Black	38	42	19.4	21	27.	29
Hispanic	25	33	35.5	38	31	36
Asian	0	0	6.5	0	4	0
Other	0	0	3.2	0	2	0
MEDICAL HISTORY						
Cardiovasc.	79	79	84	82	82	81
Respiratory	17	13	19	41	18	29
GI	33	13	26	41	29	29
Endocrinologic	13	21	23	18	18	19
Musculoskeletal	21	17	26	29	24	24
Neurologic	50	42	39	27	44	33
DISEASE CATEGORY						
Segmental Glomeruloscler.	17	20	16	38	16	31
Dysplasia or hypoplasia	17	13	32	12	26	12
Inherited/congenital	4	0	10	3	7	2
Glomerulonephritis	17	25	13	18	15	21
Obstructive uropathy	21	25	10	15	15	19
Reflux nephropathy	8	4	7	0	7	2
Cystic disease	4	0	3	6	4	3
Other	4	4	0	6	2	5
Hemolytic uremic syndrome	0	4	3	0	2	2
Pyelonephritis	0	4	0	3	0	3
Unknown	8	0	7	0	7	0
Prior immunotherapy	54	33	26	35	38	35
Prior EPO therapy	13	8	7	9	9	9
Current hypertension	54	67	45	44	49	53
Current anti-hypert. medication	54	75	48	41	51	55

The figures indicate the % of positive subjects in the column category.

All figures were rounded off the nearest whole number. For age, sex and race categories (categories are listed vertically and separated by black lines) the columns add up to 100%. For other categories there is overlap of disease or medical problems and % is > 100%.

(Sources - volume 4, tables 4.1; 5.1; 5.3; and 5.4)

Concurrent medications: Tables in section 10.1 (source- appendix E 13-1) were reviewed. There were no substantial differences in concurrent medications during the study.

4. EFFICACY RESULTS- PRIMARY ENDPOINTS:

At the end of the double blind phase there was a sharp difference between the arms with respect to attainment of target hct, mean hematocrit level, and number of transfusions/patient indicating a significant treatment effect.

In contrast, at the end of the titration phase when both arms had been exposed to erythropoeitin (EPOETIN arm week 12 and CONTROL arm week 24) there were comparable increments above the starting baseline. The two arms were approximately equal with respect to attainment of target hematocrit, mean hematocrit, number of transfusions//patient and fraction of subjects who were transfusion independent.

At the end of maintenance phase the doses were comparable in both arms and hematocrit was increased-above-the-starting-level in almost all subjects. Individual endpoints are discussed in detail below.

Statistical analysis of primary endpoints: The table below outlines the four prospectively defined endpoints. The major statistical analyses for efficacy were comparisons between the two arms for significant differences - using the first three of these endpoints, namely, attainment of target hematocrit, mean % hematocrit and mean number of transfusions/patient/four weeks. Attainment of target hematocrit was calculated as the % patients achieving success/lack of success with a "success" event countable at any time during the double blind phase. Mean hematocrit comparisons were at end of the double blind phase (average of last three hematocrit values taken during last week of double blind phase) as was the number of transfusions per patient/ over last four week period (source- appendix C.1, C2 and C3 in volume 7).

CBER statistical review of these data fully agree with the the sponsors conclusions - essentially that there were highly significant differences as a direct result of the treatment effect (see statisticians report). In addition to repeating the calculations using the prospectively declared endpoints a number of other factors were considered by CBER.

- ***The attainment of target hematocrit had serious limitations as a direct measure of treatment effect since unconfirmed observations of "success" were possible as a result of RBC transfusions or laboratory error or variation (see discussion below and under CONCISE SUMMARY). CBER reanalyzed the same data using an increase of hematocrit 6% or > as the sole endpoint. A time to event analysis was performed. The results continue to support a significant treatment effect of Epoetin in increasing the hematocrit (see Statistical Reviewer's Report).***
- ***Mean hematocrit was calculated at the end of the double blind period both for the subpopulation with full 12 week data (EPOETIN arm 51 subjects and CONTROL arm 52 subjects) and for all patients with last value carried forward ; results were similar (see Statistical Reviewer's report).***
- ***The secondary endpoint of transfusion independence was considered important and included in evaluation of the primary endpoints in evaluating treatment effect. It was consistent with a significant treatment effect for Epoetin.***
- ***The prospective endpoint of mean hematocrit comparison of the arms was viewed as — since the baselines for the arms were similar. However the actual change in each arm- as determined by the difference between the end-of double-blind study value and baseline value- was considered to have advantages over the prospectively designated choice of comparing end phase values. CBER analysis employing change of hematocrit showed a significant treatment effect (see Statistical Reviewer's report).***

SUMMARY OF FOUR PRIMARY ENDPOINTS and STATISTICAL ANALYSIS

Endpoint	EPOETIN arm	CONTROL arm	Sponsor's Statistical analysis	CBER Statistical Analysis
ATTAINMENT OF TARGET HCT[1]				
# subj.attaining target hct/total # subj. at end of double blind phase (%)	53/55 (96)	33/57[2] (58)	Fisher's Exact test p=0.001	Confirmed using same test
# subj. attaining target hct /total subj. at end Epoetin titration phase (%)	53/55 (96)	43/50 (86)		
MEAN % HEMATOCRIT				
at baseline	22.0±3.5	21.5±3.3		
at end of double blind phase	31.5±5.9	22.4±4.2	Two sided t test p=<0.001	Data differed but not enough to alter results
at end Epoetin titration phase	31.5	30.4		
during Epoetin maintenance phase	29-32.5	29-32.5		
MEAN NUMBER TRANSFUSIONS /PATIENT/ FOUR WEEKS				
at baseline	0.44	0.52		
at end double blind phase	0.21	0.40	Wilcoxon rank sum and CMH were both p=0.01 or <	Data differed but not enough to alter results
at end Epoetin titration phase	same as above	0.07		
at end Epoetin maintenance phase	0.05	0.00		
MEAN MAINTENANCE DOSE (maintenance phase)	119 U/kg	137 U/kg	Not analyzed	Not analyzed

[1]Target hematocrit was a hct between 30-36% or a rise of > 6% over the baseline hct at any time during the first 12 weeks (double blind phase) of study. [2] There were 57 evaluable subjects rather than 58 enrolled patients; patient — in CONTROL arm lacked baseline and interval hematocrit values. The end of double blind phase was week 12 for both arms; the end of Epoetin titration phase was week 12 for EPOETIN arm and week 24 for CONTROL arm; the end of Epoetin maintenance phase was week 36 for EPOETIN arm and week 48 for CONTROL arm.

Attainment of target hematocrit: During the double blind phase a statistically significant higher fraction of EPOETIN arm subjects attained the target hematocrit(EPOETIN arm 96%, CONTROL arm 58%). As anticipated when the CONTROL group was crossed over and titrated with Epoetin a comparable fraction of patients reached the target hematocrit. When the data from the two study groups are combined for attainment of target hematocrit by end of Epoetin titration (EPOETIN arm week 12 + CONTROL arm week 24), 91% or 96/105 of children attained the target hematocrit.

The surprisingly high fraction of CONTROL arm patients (n= 33/ 57) who reached target levels at the end of week 12, before they received Epoetin, requires comment. Mean hematocrit levels of the CONTROL group did not increase during the double blind phase. Several factors account for the inconsistency. Firstly, the number of RBC transfusions/per patient given to the ~~EPOETIN~~ Control group during the first 12 weeks, was higher , namely 1.3 (3.0 HD and 0 PD) EPOETIN arm vs. 3.4 (4.1 HD and 2.8 PD) CONTROL arm artificially elevating the hematocrit above the target level in many cases and registering a subject as having reached the target level . Attainment of the target hematocrit was defined as positive if it occurred at any time during the 12 weeks even when it was on the basis of transient elevations attributable to transfusions or to laboratory variations. When the graphed week by week hematocrit and transfusion levels for each patient were examined (source-volume 26, appendix F1), most CONTROL patients who reached target hematocrit did so transiently and failed to maintain a consistent level nor show the incremental rise characteristic of Epoetin- treated subjects. In contrast the EPOETIN group showed a pattern of gradual but sustained rise in hematocrit vs.time.

Mean hematocrit levels of the two arms: Hematocrit rose sharply during EPOETIN titration. Baseline hematocrit values for the EPOETIN and CONTROL arms were 22.0 % and 21.5 % and increased by 9.5 and 0.9 % respectively by end of week 12 demonstrating a treatment effect. When CONTROL arm subjects were crossed over and titrated with Epoetin for 12 weeks, hematocrit increased by 8% to 30.4 %. During the maintenance period the hematocrit remained at the higher level.

Changes in transfusion requirements and transfusion independence: The number of transfusions per patient decreased in response to Epoetin treatment in the EPOETIN arm during the double blind phase and in the CONTROL arm during Epoetin titration (weeks 12-24). Individual patients showed hematocrit rises as early as 2-4 weeks after therapy began.

At baseline 65.5 and 62.1 % of EPOETIN and CONTROL groups were transfusion independent. By the end of the study 31/31 CONTROL subjects and 37/39 of EPOETIN arm subjects were transfusion independent. [Transfusion independence was defined as < 5 cc of whole blood or packed red cells /kg patient weight in any consecutive 4 week period]. This suggested that most children will respond to Epoetin despite differences in dose needed and responsivity. Differences between subjects treated with different modes of dialysis/different routes of administration (PD patients received SC Epoetin while HD patients received IV Epoetin) are discussed next in section 5.

The mean number of transfusions/patient/four weeks, the % of transfusion independent patients, and the mean hematocrit all improved concomitantly (see table).

CONCOMITANT CHANGES IN HEMATOCRIT, MEAN NUMBER OF TRANSFUSIONS/PATIENT, AND TRANSFUSION INDEPENDENCE SHOWN FOR EACH FOUR WEEK PERIOD OF STUDY

	Epoetin	Epoetin	Epoetin	Epoetin	Control	Control	Control	Control
Period ending week	# patients remaining in study	Mean # transfusions /pt/4 wk	% transfusion independent (n=)	Mean hct	# patients remaining in study	Mean # transfusions/ patient/ 4wk	% transfusion independent (n=)	Mean hct
0	55	0.44	65.5 (36)	22.0	58	0.52	62.1 (36)	21.5
4	55	0.11	89.1 (49)	26.8	57	0.46	63.2 (36)	21.7
8	54	0.19	92.6 (50)	31.2	53	0.64	62.3 (33)	22.4
12	52	0.21	92.3 (48)	31.5	52	0.40	65.4 (34)	22.4
16	50	0.04	98.0 (49)	32.4	50	0.24	80 (40)	25.8
20	49	0.06	95.9 (47)	32.0	45	0.07	95.6 (43)	29.7
24	47	0.06	95.7 (45)	30.0	45	0.07	95.3 (43)	30.4
28	45	0.00	100 (45)	30.8	36	0.00	100 (36)	32.3
32	42	0.02	97.6 (41)	30.6	34	0.00	100 (34)	31.5
36	39	0.05	94.9 (37)	30.7	34	0.00	100 (34)	29.4
40-48					31	0.00	100 (31)	29.3

Parentheses are # of patients.[Source- volume 1, attachment 3.3-12 and volume 6, appendix B1.2.6].

5. EFFICACY RESULTS -COMPARISONS OF STRATIFICATION SUBSETS

Data from the six stratification subsets were reviewed to determine if age or mode of dialysis influenced responsivity to Epoetin. Differences in the age distribution between PD and HD subjects make interpretation of any trend more difficult (see first table below). Initial comparison between stratification subsets for attainment of target hematocrit at end of Epoetin titration (see second table below) showed no differences . In contrast, comparison of mean hematocrit change (see third table below) suggested that the hematocrit increased faster in PD as compared to HD subjects (see bold values for hematocrit in Epoetin titration row in 3rd table below). The last table (fourth and lowest table in this section) compares change in hematocrit at four weekly intervals for HD and PD in both arms and confirms the impression that the response to Epoetin is more rapid in the PD as opposed to HD subjects. The differences observed between HD and PD were marked during Epoetin titration and tended to lessen and disappear during the maintenance phase.

CBER analyzed the differences between HD and PD response to Epoetin titration using as the endpoint (success) an increase in hematocrit of 6% or more above the baseline value;success was plotted as time to event and analyzed using the Log-Rank test. If baseline hematocrit was not available for the first 7 days the patient was regarded as unevaluable. A hematocrit value which demonstrated success had to be confirmed on the next hematocrit which either showed the same 6% or greater increase above baseline and was no more than 1% less than the prior hematocrit value. The following data were obtained. HD patients had median time to response of 69 days in both arms while PD patients had median times of 26 days in EPOETIN arm and 38 days in CONTROL arm. The difference between HD and PD was highly significant (see Statistical Reviewer's Report).

AGE DISTRIBUTION IN TWO ARMS BY MODE OF DIALYSIS

age bracket	EPOETIN arm baseline number		CONTROL arm baseline number	
	HD	PD	HD	PD
0-<5	0	5	1	11
5-<15	13	16	12	19
15<18	11	10	11	4
totals	24	31	24	34

SIX STRATIFICATION SUBSETS COMPARED FOR ATTAINMENT OF TARGET HEMATOCRIT

	Age bracket	Epoetin titration in EPOETIN arm-wks 1-12	Epoetin titration in CONTROL arm-wks 12-24	Totals
		# attain target hct/ /# in arm end of week 12	# attain target hct/ # in arm end of week 24	# attain target hct/ # in arm
HD	0-<5	0/0	0/0	0/0
HD	5-<15	13/13	8/10	21/23
HD	15-<18	9/11	9/11	18/22
HD	all	22/24	17/21	39/45
PD	0-<5	5/5	7/9	12/14
PD	5-<15	16/16	16/16	32/32
PD	15-<18	10/10	3/4	13/14
PD	all	31/31	26/29	57/60
HD+ PD	0-<5	5/5	7/9	12/14
HD +PD	5-<15	29/29	24/26	53/55
HD+ PD	15-<18	19/21	12/15	31/36
HD + PD	all ages	53/55	43/50	96/105

(Source - Section 3.3.3 in volume 1, attachment 3.3.6)

SIX STRATIFICATION SUBSETS COMPARED FOR CHANGES IN HEMATOCRIT

Dialysis type	Age bracket	Baseline hct	Hct-end Epoetin titration	Change in hct	Baseline hct	Hct at end Epoetin titration	Change hct
		EPOETIN	EPOETIN	EPOETIN	CONTROL	CONTROL	CONTROL
		mean hct (n)	mean hct (n)	mean hct (n)	mean hct (n)	mean hct (n)	mean hct (n)
HD	0-<5	(0)	(0)	-	27.9 (1)	(0)	-
HD	5-<15	21.2 (13)	28.6 (13)	7.4	20.0 (10)	25.5 (8)	5.5
HD	15-<18	19.6 (10)	26.2 (10)	6.5	22.5 (11)	29.8 (9)	7.3
HD	all	20.5 (23)	27.5 (23)	7.0	21.6 (22)	27.8 (17)	6.2
PD	0-<5	23.0 (5)	30.5 (5)	7.5	20.0 (10)	236.7 (8)	6.7
PD	5-<15	23.9 (16)	34.5 (16)	10.6	21.1 (18)	36.7 (15)	15.6
PD	15-<18	21.1 (10)	36.2 (10)	15.1	26.1 (4)	30.2 (4)	4.1
PD	all	22.9 (31)	34.4 (31)	11.5	21.4 (32)	32.8 (27)	11.4
HD+ PD	0-<5	23.0 (5)	30.5 (5)	7.5	20.7 (11)	26.7 (8)	6.0
HD +PD	5-<15	22.7 (29)	31.8 (29)	9.1	20.7 (28)	32.8 (23)	12.1
HD+ PD	15-<18	20.3 (20)	31.2 (20)	10.9	23.5 (15)	30.0 (13)	12.5
HD+ PD	all ages	21.9 (54)	31.5 (54)	10.4	21.5 (54)	30.8 (44)	9.3

(Source- Appendix B1.2.1 in volume 6 is the final study report rather than the Summary of efficacy (SOE) from which the majority of information was obtained . This was done to provide comparable information on both study arms (SOE lacked comparable CONTROL arm data).) Baseline hct is the pre-treatment measure closest to first dose of agent. The EPOETIN arm hct at 12 weeks was the last available measurement during the double blind phase. The CONTROL arm measurement is the last available hct in the 24 week treatment phase. Attainment of target hct in last column refers to prospectively designated primary endpoint of increase of hct equal to or > 6% or a hct > 30%.

FOUR WEEKLY COMPARISONS OF MEAN HCT OF HD AND PD PATIENTS

	HD	HD	PD	PD
EPO/Placebo end of study period week	EPO mean hct (N)	Placebo mean hct (N)	EPO mean hct (N)	Placebo mean hct (N)
Baseline	20.5 (23)	21.6 (22)	22.9 (31)	21.4 (32)
Epoetin titration phase				
4/16	24.4 (23)	23.4 (17)	28.6 (31)	27.3 (27)
8/20	27.9 (23)	26.8 (17)	33.7 (31)	31.5 (27)
12/24	27.5 (23)	27.5 (16)	34.4 (31)	32.9 (26)
Maintenance - first 12 wk				
16/28	29.0 (20)	29.0 (12)	34.8 (27)	34.3 (20)
20/32	30.1 (20)	30.9 (12)	33.3 (27)	31.8 (20)
24/36	29.4 (20)	31.0 (12)	32.0 (27)	28.5 (20)
Maintenance -last 12 wk				
28/40	30.0 (17)	30.0 (10)	31.4 (24)	28.6 (16)
32/44	29.2 (17)	29.2 (10)	31.6 (24)	29.7 (16)
26/48	30.2 (16)	30.2 (10)	31.3 (23)	31.6 (13)

EPO/Placebo- refers to the study week of patients on EPOETIN arm and Placebo arm

Epoetin doses: There was no difference in median dose of Epoetin needed to achieve target hematocrit between the EPOETIN and CONTROL arms and between HD and PD patients. On the other hand it is noted that the median maintenance dose for PD patients for the last two weeks of the study was 76 Units/kg per week for PD patients as compared to 167 Units/kg/week for HD patients. There was no significant difference in the Epoetin needed to reach the target hct between arms (see below) or for HD vs. PD patients but there was a difference in maintenance dose. . EPO-9118 study of pediatric patients on maintenance Epoetin showed similar maintenance dose differences between HD and PD children.

MEDIAN DOSE TO ACHIEVE TARGET HEMATOCRIT AFTER EPOETIN TITRATION

	Dose in Units/kg/week all patients	Dose in Units/kg/week HD patients	Dose in Units /kg/week PD patients
EPOETIN ARM	143	144	140
CONTROL ARM	144	146	142

MEDIAN DOSE TO ACHIEVE TARGET HEMATOCRIT DURING MAINTENANCE PHASE

	Dose in Units/kg/week all patients	Dose in Units/kg/week HD patients	Dose in Units /kg/week PD patients
EPOETIN ARM	119	145[1] or 167[2]	97[1] or 76[2]
CONTROL ARM	137		

[1] Mean dose during entire maintenance period calculated by sponsor and found in SOE
[2] Mean dose during last two weeks of maintenance period calculated by CBER

6. RESULTS- SECONDARY EFFICACY AND SAFETY ENDPOINTS

Secondary endpoints included; many were quantitative.

- Transfusion independence
- Epoetin alfa dose needed to achieve target level in U/kg/week
- Rate of hct rise in points /week
- Quality of life and Cognitive function
- Growth assessment and sexual development
- Endocrine function incl. thyroid
- Ferritin, transferrin saturation
- Dose of supplemental iron needed
- Blood pressure
- Serum chemistry values
- Nutrition assessment
- Frequency and duration of hospitalization
- Reticulocyte count

Safety endpoints included:

- Incidence AE
- Laboratory serum chemistries and hematologoy
- Vital signs including blood pressure

Transfusion independence: At baseline 36/55 (65.5%) of HD and 36/58 (62.1%) of PD patients were transfusion independent. At end of the double blind period, 92% (48/52) of EPOETIN arm subjects were transfusion independent as compared to 71% (37/52) in the CONTROL arm [see IIa, section 4]. The difference was statistically significant. After the CONTROL arm was crossed over (and received Epoetin) the percentage of transfusion independent patients in the CONTROL rose to 95% (41/43) comparable to the results in the EPOETIN arm.

Ferritin and transferrin saturation: Transferrin saturation decreased during the first four weeks of the study (mean changed from 40.8% to 21.0%- 26.5% ± 20.0%) and then remained stable. At the end of week 12 the EPOETIN arm was 29.3% vs CONTROL arm 43.2% - p= <0.001. The average transferrin saturation remained above 20% for the course of the study. Ferritin concentrations did not differ between the two arms. In general more PD than HD patients received iron supplementation. Oral supplemetation was more frequent than IV iron.

Cognitive testing: 111/ of 113 patients were tested at baseline and three month intervals. Striking developmental delays were present at the baseline and persisted through the testing period. Improvement was noted after 6-9 months of therapy. The sponsors are forthright in indicating that results were not definitive and interpretation required caution. No conclusions could be drawn from the data .

Nutrition assessment: A diary was kept on three consecutive days and the analyzed by a software program comparing the results with paired t test. The results showed a modest increase in energy intake (61.7 CONTROL vs 70.0%, p= 0.069 EPOETIN-% RDA in intake) in the last 12 weeks of therapy.

Growth and Sexual development: Growth was measured by changes from baseline in height, weight and head circumference. No significant differences were noted. Skeletal maturity used radiographs of the left hand/wrist and showed increase in skeletal maturity commensurate with increase in chronological age but no acceleration or maturity to compensate for the retarded development present in the children at start of study.

Sexual development was measured according to Tanner staging and revealed no significant differences between treatment groups.

Other measurements: No differences are reported for any other laboratory measurements .

PART IIb- STUDY EPO-9118 REVIEW

I STUDY DESIGN

Overview and Experimental design: Study EPO-9118 was a single arm, non-randomized, uncontrolled study of 74 children (40 males and 34 females) with CRF on either hemodialysis or peritoneal dialysis- all of whom had recently completed participation in study EPO-9002. The purpose of the study was to evaluate the safety and performance of Epoetin therapy in children for longer than the 24 weeks on maintenance therapy of study EPO -9002. Study duration was 12 months but patients were permitted to exit . Stratification was by mode of dialysis (HD or PD) and by age brackets 0-<5, 5-<15, and 15-<18, or > 18 years.

Study subjects: There were 74 subjects enrolled at 13 sites. Exclusion criteria included systemic hematologic diseases and cytotoxic/ immunosuppressive therapy.

Planned analyses: The primary efficacy endpoints were hematocrit and Epoetin alfa dose and frequency. Hematocrit was judged by the fraction of patients, during four week intervals, who remained within the target hematocrit range of 30-36%. Secondary endpoints included transferrin saturation and ferritin concentration, the fraction of patients whose transferrin saturation was < 20%, the number of transfusions, and growth and sexual development. Safety variables included AE, blood pressure , serum chemistries , concomitant medications. Most primary and secondary analyses were descriptive.

Dosing schedule: All patients entered the study at their current (EPO-9002) dose of Epoetin alfa, frequency and route of administration. PD patients received subcutaneous (SC) Epoetin alfa injections usually given by a parent or guardian; HD patients received IV agent through the extracorporeal tubing during the last 5 minutes of dialysis. Dose adjustments were designed to stabilize hematocrit within target range of 30-36%. If HD patients required a dose reduction, dose was decreased by 10 Units/kg maintaining the same frequency of administration and using 2 week or greater intervals between dose reductions until the hematocrit was in the target range. Dose increases were 10 Unit/kg with intervals of 2 weeks. In PD patients dose reduction was by elimination of one dose/week with two week intervals between dose decreases. Increases in dose in PD patients were in 10 Unit/kg increments with two week intervals. There was a maximum dose of 10,000 Units or 200 Units/kg for both HD and PD patients.

Monitoring: The experimental schedule and tests are listed on study calendar -see enclosure 2. The schedule was similar to EPO-9002. Routine studies included history and physical examinations, chest xray, complete blood counts and differential, serum iron levels, transferrin saturation, platelet and reticulocyte determinations, clinical chemistry including coagulation studies. Erythropoeitin antibody determinations were performed at intervals (see calendar). Growth assessment, nutritional status, thyroid function, cognitive and quality of life testing were analyzed separately using a battery of tests. Safety data and secondary endpoint data collected included adverse events, number of transfusions of blood, number of days of hospitalization, changes in dialysis strategy and concomitant medications.

Procedures: Concomitant medications were permitted at the discretion of the physician; the only exceptions were other investigational agents, and immunosuppressives/androgens for hemodialysis patients. If during the study the patients transferrin saturation fell < 30%, patients received oral iron supplementation at a dose 1-2 mg/kg and parenteral iron if oral supplementation failed. Blood pressure was

closely monitored. It was recommended that the dose of Epoetin alfa be decreased if the hematocrit increase exceeded 4% in a 2 week period.

2. CONDUCT OF THE STUDY

Patient disposition: The study duration was 12 months but was administratively terminated early by sponsor creating a fraction of patients whom were studied for less time; the mean duration of patient study was 36.9 weeks (range 2-84 weeks). The reasons for discontinuation include 47 patients discontinued study because of premature truncation of the experimental program; 21 because of transplants and 6 for other reasons (see second table below). Thirty-three subjects discontinued participation after 6 months on therapy leaving 41 patients. By 12 months only 26 or roughly a third of children remained on study.

Period of study	Status	HD	PD	All
0-6 months	Enrolled	35	39	74
	Patient discontinued	7	7	16
	Study Administratively discontinued by sponsor	8	9	17
6 to 12 mos	Completed 6 months	18	23	41
	Patient discontinued	4	3	7
	Study Administratively discontinued by sponsor	2	6	8
12-18 mos	Completed 12 months	12	14	26
	Patient discontinued	3	1	4
	Study Administratively discontinued by sponsor	4	6	10
18-24 mos	Completed 18 months	5	7	12
	Study Administratively discontinued by sponsor	5	7	12

Reasons for discontinuation	HD	PD	total
Study administratively discontinued by sponsor	19	28	47
Kidney transplant	11	10	21
Other	5	0	5
Request to withdraw	0	1	1
Total	35	39	74

3. RESULTS- DEMOGRAPHIC/CLINICAL FEATURES

	HD n=	HD %	PD n=	PD %	total n=
Male	20	57.14	20	51.28	40
Female	15	42.86	19	48.72	34
RACE Caucasian	6	17.4	14	35.90	20
Black	14	40.00	9	23.08	23
Hispanic	14	40.00	15	38.46	29
Asian & other	1	2.86	0	2.56	2
AGE<5 years	0	0	6	15.38	6
5-<15 years	19	54.29	25	64.10	44
15-<18 years	11	31.43	6	15.38	17
18 years or >	5	14.29	2	5.13	7

Cause of CRF	HD %	PD %
Focal segmental glomerulosclerosis	29	21
Dysplasia/hypoplasia	17	18
Glomerulonephritis	23	15
Obstructive uropathy	20	21

4. RESULTS- ENDPOINTS

Hematocrit values and target range: For the entire treatment period an average of 51% of patients had hematocrit values in the 30-36% range.The percent of patients in the target range at four week intervals is shown below.

PATIENTS WITH HEMATOCRITS IN THE TARGET RANGE

Week	Total number of patients	Percent patients in target range	weeks	Total number of patients	Percent patients in target range
1-4	69	34.8	45-48	26	57.7
5-8	71	42.3	49-52	24	62.5
9-12	64	42.2	53-56	22	68.2
13-16	57	54.4	57-60	17	47.1
17-20	43	51.2	61-64	17	47.1
21-24	39	46.2	65-68	12	41.7
25-28	37	45.9	69-72	13	53.8
29-32	32	40.6	73-76	12	58.3
33-36	32	37.5	77-80	8	62.5
37-40	31	41.9	81-84	6	83.3
41-44	29	51.7			

Results- Epoetin alfa dose and frequency: Most patients during the study received 50-200 Units/kg per week with the most common (median) dose being 180 Units/kg per week given TIW (n=43/74). Changes in dosing were most frequent during the first 36 weeks of study with many patients changing the dose one or more times. After 36 weeks fewer dose changes were observed.

	HD	PD
Average monthly hematocrit	30.9% (range 29.0% to 32.1%)	31.9% (range 28.6 to 35.5%)
Median Epoetin dose range during study	143-340 Units/kg/week	58-117 Units/kg/week
Median dose of Epoetin during study	174 Units/kg/week	89 Units/kg/week

Results-transfusions: Fourteen or 19% of the 74 patients received 28 transfusions- an average of 2 transfusions per transfused patient or 0.4 transfusions per patient if all patients are considered. Transfusion volumes for the 14 children who received blood are shown in the table below.

Patient	Number of transfusions	Total cc/kg transfused
262	1	5.0
361	4	31.3
366	3	29.2
369	1	12.0
662	6	88.9
962	1	missing
964	2	12.9
1261	2	205.3
1368	1	9.5
1369	1	5.8
1566	1	13.9
1567	1	6.6
1568	1	7.3
1660	3	24.5

(Source was volume 31, section 9.6.2 of study report, table D, page 38)

Results-other endpoints: Mean monthly transferrin saturation range was 23.7% to 35.2% during the study . From 13.8% to 48.2%. of patients had transferrin saturation levels equal to or < 20%. HD patients generally had lower transferrin saturation; however, there was no difference in the number of HD and PD patients who received iron supplementation.

Epoetin maintenance treatment was not reported to have a discernible effect on growth and development, sexual development, bone age or cognitive function.

Safety: The AE data are reviewed as integrated data in part III of this report. Inspection of the EPO-9118 safety data for events of interest/concern does not suggest differences from data reported for adults and that data summarized in the Integrated Safety Analysis. These data are similar to previously reported incidences of events/patient year ;selected figures include access infection 0.46, access complication 0.49, influenza like symptoms 0.36, hypertension 0.49, convulsions 0.43.

PART IIc- STUDY EPO -8905 REVIEW

1.STUDY DESIGN

Overview and experimental design: Study EPO-8905 was a two arm, placebo controlled, randomized study of 10 patients with CRF on hemodialysis ranging in age from 7 to 18 years . One arm received placebo , the other Epoetin alfa IV 150 Units/kg/per week given TIW. Dose was adjusted to attain a target hematocrit of 32-38%. At the end of the 12 week double blind period the study was unblinded. Placebo arm patients were then crossed over to a 12 week phase of Epoetin titration while treatment arm subjects were placed on a maintenance schedule using the same 32-38% target hematocrit range . At 24 weeks all patients were placed in a maintenance phase. Dose adjustment was by 10 Units/kg increments or decrements. Patients could remain on study for up to 2 years.

Study subjects: All study subjects were children with chronic renal failure on hemodialysis for at least three months and under the age of 18 at time of study entry. Baseline hematocrit had to be < 30%.

Procedures and dosing schedule: With few exceptions the study procedures were similar to EPO-9002. Among the differences were the target hematocrit range which was 32-38% as compared to 30-36% for the EPO-9002 study;

Monitoring: Similar to study EPO-9002-see enclosure 2 for study calendar.

Endpoints and Planned analyses: Endpoints were comparative hematocrit values and volume of transfusions.

2. CONDUCT OF THE STUDY

Patient disposition:

Study phase	Results	EPOETIN arm	CONTROL arm
Double blind phase wks 1-12	Entered	4	6
	Discontinued	0	1*
Unblinded phase wks 12-24	Entered	4	5
	Discontinued	1*	0
Completed study		3	5

* Discontinued because of renal transplantation

3. RESULTS-DEMOGRAPHIC FEATURES:

Variable	EPOETIN arm	CONTROL arm
Age -mean + range	16.5 (15-18)	10.7 (7-16)
Sex	2 male/2 fm	4 male/2 fm
Current hypert.	3/4	4/6
Diabetic	0/4	0/6

Three/10 patients had glomerulonephritis; 1/10 polycystic kidney dis.; 6/10 other urologic problems

4. RESULTS-ENDPOINT.

BETWEEN GROUP COMPARISONS OF HEMATOCRIT

	EPOETIN arm		CONTROL arm		p value
	n	het%	n	het %	
Baseline	4	21.9	5	21.8	0.899
Week 4	4	24.4	5	19.6	0.001
Week 8	4	28.2	5	22.4	0.031
Week 12	4	29.6	5	22.9	0.023

WITHIN GROUP COMPARISONS OF HEMATOCRIT

	n	het%	Difference from baseline	p value
EPOETIN				
Week 4	4	24.4	2.5	0.066
Week 8	4	28.2	6.3	0.049
Week 12	4	29.6	7.7	0.062
CONTROL				
Week 4	5	19.6	-2.1	0.093
Week 8	5	22.4	0.6	0.795
Week 12	5	22.9	1.1	0.537

Transfusion: During the first 4 weeks of study 1/4 EPOETIN arm and 4/5 CONTROL arm subjects were transfused. During the last 4 weeks of the double blind phase none of the EPOETIN arm but all CONTROL arm subjects required transfusion.

PART IId- STUDY EPO -8702 REVIEW

Overview and experimental design: Study EPO-8702 was a single arm, non-randomized, non-placebo controlled study of five children with chronic renal failure receiving peritoneal dialysis.Patients received 150 Units/kg/per week subcutaneously TIW for 12 weeks. The target hematocrit of 35% or an increase of 10 hematocrit % units over baseline.

Results: The study was a safety and tolerance study in children receiving peritoneal dialysis and a preliminary activity study and as such the numbers were too small for statistical analysis. All five subjects responded to Epoetin therapy with increases in hematocrit and a lessened number of transfusions. Safety data were included in the integrated safety analysis.

PART III

INTEGRATED SAFETY ANALYSIS

1. BACKGROUND AND METHODOLOGY FOR SAFETY REVIEW

Sources of data : Integrated safety data for pediatric patients on dialysis were collected from the four clinical trials as shown below. Two analyses were performed ; they are referred to as the " double blind analysis" and "all exposure analysis". The double blind analysis" included all patients who received at least one dose of Epoetin or placebo during the first 12 weeks of study. It was an intend- to -treat analysis and includes all patients including those who had less than 12 weeks of study time. The " all exposure analysis" includes subjects who received at least one dose of Epoetin alfa. This amounted to 135.7 patient years of drug exposure. The" all exposure analysis" group had a smaller number of patients than the double blind series since it excluded the 8 EPO-9002 subjects and one EPO-8905 subject who were randomized to the placebo and dropped out before receiving Epoetin. Subjects first enrolled into EPO-9002 and then crossed over into EPO-9118 maintenance study were only counted once.

STUDY	DOUBLE BLIND ANALYSIS	ALL EXPOSURE ANALYSIS
	# subj.	#subj.
EPO-8702a	0	5
EPO-8905a	10	9
EPO-9002	113	165
EPO-9118	0	174c
Totals	123	119

a one patient withdrew and did not crossover to Epoetin treatment

b eight patients withdrew and did not crossover to Epoetin treatment

c 74 patients who completed EPO- 9002 and rolled over into EPO-9118 were counted only once under EPO-9002 in "all exposure analysis"

Collection of data: A modified dictionary (WHO-ART) was used by medically trained Amgen staff to classify Investigator descriptions of AE into preferred terms and body systems. When available information was insufficient the AE was left uncoded and a verbatim description was provided.

SUMMARY CHART OF ADVERSE EVENTS

TYPE OF ADVERSE EVENT	Column A DOUBLE BLIND ANALYSIS	Column B DOUBLE BLIND ANALYSIS	Statistical analysis of columns A vs.B	ALL EXPOSURE ANALYSIS
subjects exposed to (n)	Epoetin (59)	Placebo (64)		Epoetin (119)
DEATH # subj.	1	0		2
WITHDRAWALS DUE TO AE # subj.	0	1		0
AE by PREFERRED TERM-% subj.(n) in order of frequency				
hypertension	25.4 (15)	17.2 (11)	p=0.28 FE	44.5
vomiting	22.0 (13)	21.9 (14)	p= 1.0 FE	37.0
headache	22.0 (13)	29.7 (19)	p= 0.41 FE	44.4
myalgia	20.3 (12)	6.3 (4)	p=0.03 FE	29.4
abdominal pain	20.3 (12)	25.6 (16)	p=0.67 FE	38.7
AE by BODY SYSTEM-% subj.				
gastrointestinal	67.8	59.4	p=0.35 FE	84.9
body as whole	66.1	56.3	p=0.27 FE	79.8
nervous system	39.0	42.2	p=0.85 FE	55.5
skin & appendages	23.7	9.4	p=0.05 FE	47.1
respiratory	35.6	32.8	p=0.85 FE	60.5
SEVERE, LIFE THREATENING & FATAL AE- % subj. (n)				
all events	15.3 (9)	6.3(4)	na	21(36)
SPECIAL CONCERN AE-% subj. (n)				
convulsions/siezures	8.5 (5)	6.3 (4)	p=0.74 FE	13.3
hypertension	25.4	17.2	p=0.28 FE	44.5
vasc. access				
thrombosis	6.8 (4)	1.6 (1)	p= 0.19 FE	15.1
infection	20.3 (12)	12.5 (8)	p= 0.33 FE	na
clot	8.5 (5)	12.5 (8)	p= 0.10 FE	1.7
complication	10.2 (6)	6.3 (4)		
SERIOUS AE-% subj. (n)	47.5 (n=28)	37.5(n=24)	p= 0.264 CHI	

Figures are for % of patients who have experienced event in each column category; in some cases the number of subjects are given in parentheses.

Only Preferred term events> 5% were listed; Body System events were selected either because of their frequency or possible relationship to agent based on historical experience.FE is Fishers Exact test: CHI is chi square test: na is not applicable

(Sources of AE data- by Preferred term, by Body System, for Severe/life- threatening and fatal AE, and for AE of special concern are Volume 2, attachments 3.4-5-8)

2. DEATHS: There were two deaths during the study; both involved cardiac arrest . Neither was considered by the investigators to be related to Epoetin. Data and a clinical precis and a summary of the autopsy report for patient — failed to link Epoetin to the patient death; subject — had multiple congenital abnormalities. Patient — likewise died of uncertain causes not clearly related to the experimental agent.

Patient	EPO study	age yrs	Days on study	Cause death	Days since last dose	Cumulative dose U/kg	Treatment arm	Judged related to EPO
1	8905	11	273	cardio-pulm. arrest	2	5659	CONTROL	no
1	9002	0.5	56	cardiac arrest	0	1078	EPOETIN	no

Patient — was a 6 month old male with chronic end stage renal disease, microcephaly, pseudohermaphrodism and developmental delays consistent with the DRASH syndrome. He was receiving peritoneal dialysis and had been enrolled on the EPOETIN study arm for 8 weeks at the time of his death. Other conditions he suffered from included Wenckebach phenomenon, hypertension thought to be volume related, cryptorchidism, hypospadias, and developmental delay. He had history of repeated fevers with negative cultures. He was admitted to the hospital where he died one day later with a temperature of 40.8 C. Admission examination was non-contributory and the only laboratory abnormality was a shift to the left of his white cells at the time of hospitalization. In the hospital the child became lethargic with a slow pulse and died shortly afterward; the cause of his death was uncertain but the possibility of overwhelming sepsis was raised.Autopsy was consistent with end stage renal disease (small fibrotic kidneys) and showed bilateral pulmonary congestion and bilateral effusions. There was generalized lymphoid depletion, focal pancreatic hemorrhages, a right perirenal hematoma and developmental delay. As described earlier, hypospadias and cryptorchidism were present.

Patient —— was a 2.5 year old male who had received approximately one year of Epoetin. He expired two weeks after study EPO-9118 closed and 2 days after his last dose of Epoetin. At time of terminal hospitalization he presented with respiratory distress, diarrhea and dehydration. .A"respiratory culture" was positive for Aspergillus. During hospitalization his condition deteriorated. There was a suspicion of sepsis. Death occurred 7 days after admission. The cause of his death was attributed to respiratory failure with possible sepsis and judged by investigator not to be Epoetin related.

3. WITHDRAWAL BECAUSE OF INTOLERABLE AE AND DROPOUTS:

The only listed withdrawal because of intolerable AE was in the CONTROL arm and occurred *before* the patient received Epoetin (scheduled to start week 12). Dropouts are reviewed in section II, 2 CONDUCT OF THE STUDY.The discontinuation/dropout data do not suggest an undue number of dropouts due to drug effect during either the double blind or maintenance phases.

4. SEVERE, LIFE THREATENING AND FATAL AE

The number of subjects with severe, life threatening and fatal events are listed in the table below. The preferred term for AE events was used. Multiple events occurred in subjects and as a consequence the number of affected patients and the number of type of events are often different. The most frequent or relevant events are listed under"all exposure" analysis. In the comparative analysis between EPOETIN and CONTROL arms at end of the double blind period there is no obvious discrepancy to suggest drug-induced AE. The "all exposure" analysis is evaluated in section 6 by comparison to published figures for incidence.

SEVERE, LIFE THREATENING OR FATAL EVENT	Double blind analysis EPOETIN ARM (n-59)	Double blind analysis CONTROL ARM (n=64)	Rel	All exposure analysis	Rel
number events	9	6		96	
number subjects with event	9	4		36	
AE event					
Cardiac arrest	1**		N		
Cardiac failure	1*		N		
Myalgia	2		N		
Sepsis	1		N		
Azotemia	1		Y		
GI hemorrhage	1		N		
Hypertensive enceph.	1*		N		
Access complication	1		N		
AE event					
Convulsions		2	1Y/1N		
Fever		3	N		
Failure to thrive		1	N		
Granulocytopenia		2	N		
Hypocalcemia		1	N		
AE event					
Hyperkalemia				6* (3)	N
Hypertensive enceph.				4 * (3)	N
Hypertension				12 (4)	N
Ventricular arrhythmia				1 *	N
Thr vasc access/or access complication				7 (6)	N3/Y4
Convulsions/siezures				3 (3)	N1/Y2
Sepsis				3 (3)	N
Myalgia				8 (5)	N
Pancreatitis				1	N
Coagulation disorder				1	N

Figures show number of subjects with an event; parentheses show number of subjects.
Rel column indicates whether event was judged by investigator as related to Epoetin (Y) or not related (N).
Thr vasc access is thrombosis vascular access
** indicates fatal AE while * indicates life threatening AE
(Source was Appendix 3-1H , and 3-1M, volume 42-see enclosure 3)

5. AE BY PREFERRED TERM AND BODY SYSTEM: The only two preferred terms which appeared more frequently in the EPOETIN when compared to the CONTROL arm was skin and appendages and myalgia (see below).

Skin and appendages: Figures in table below shows the percent of patients with each type of skin condition. No skin AE was listed as severe or life threatening. Most are attributable to the subcutaneous injections.

	Double blind phase EPOETIN arm	Double blind phase CONTROL arm
% patients (n)	23.7 (14)	9.4 (6)
pruritus	11.9	3.1
rash	3.4	0
macular papular eruption	1.7	0

Myalgia: The comparison of the subjects at the end of the double blind phase shows a significant difference in incidence of myalgia. A patient by patient review of the 16 reported cases (12 were in EPOETIN arm and 4 in the CONTROL arm) concluded that the myalgia was of limited duration although data was missing for many subjects. Two of the 12 cases in the EPOETIN group were classified as of moderate severity. There was no change in dose/disposition of the drug in any patient. Only one case of the 12 EPOETIN arm cases was considered by the Investigators as possibly related to Epoetin. The Preferred term myalgia is broad ranging. At CBERs request the sponsor provided a list of verbatim terms from which preferred term myalgia was interpreted. The list included as enclosure 4 can be seen to cover a wide variety of medical situations.

6. AE OF SPECIAL CONCERN:

INCIDENCE EPOGEN ASSOCIATED AE IN EVENTS /PATIENT YEAR

	AE PLA 97-0006*			PDR 1994, p.502
	#events (# subj.)	# events/ yrs exposure		
Hypertension	12 (4)	12/135.7	0.088	0.75
Hypertensive encephal.	4 (3)	4/135.7		not provided
Headache				0.40
Tachycardia				0.31
Nausea/vomiting				0.26
Clotted vascular access	7 (6)	7/135.7	0.051	0.25
Shortness of breath				0.14
Convulsions/seizures	3 (3)			not provided
Myalgia	8 (5)			not provided
Hyperkalemia				0.11
Diarrhea				0.11

* all exposure analysis " had a total of 135.7 patient years of exposure

7. SERIOUS AE: The sponsor used the FDA definition of a serious event as any event which suggests a significant hazard, contraindication, side effect or precaution and included any life threatening or fatal events, any event which requires or prolongs hospitalization, any event which causes permanent disability, any known or suspected overdose, a malignancy or congenital anomaly. There was no detectable of a difference between the experimental (EPOETIN) and placebo (CONTROL) arms.

Preferred term	EPOETIN arm (n=59)	CONTROL arm (n= 64)
All	28	24
Body as a whole	13	8
Cardiovascular	4	5
Hypertension	4	5
Cardiac failure	1	0
Heart rate/rhythm	1	0
CNS/PNS	4	2
GI	11	11
Granulocytopenia	0	1
Metabolic	1	0
dehydration	0	4
hyperkalemia	0	2
hyponatremia	0	1
hypocalcemia	1	1
Musculoskeletal	0	1
Sepsis	2	2
Infection	1	1
Respiratory	2	1
Urinary	1	0
Convulsions	2	2
Thr vasc access	4	1

FIGURES ARE IN NUMBERS OF PATIENTS WHO HAD EVENT

Thr vasc access is thrombosis of vascular access.

(Sources -Attachment 3.4-9 in volume 2 and Appendix 3-1L in volume 42.)

All data are for the first 12 weeks of the study, that is the double blind phase.

8.CHANGES IN BLOOD PRESSURE (Source- volume 2, attachment 3.4-10) Monitoring of blood pressure showed a trend to a small increment in both systolic and diastolic blood press. CBER analysis showed no significant differences.. There appeared to be more blood pressure rise in HD than PD patients which could not be confirmed by statistical analysis (Wilcoxon p value = 0.047; t test p= 0.055)

9. REVIEWER ANALYSIS OF SUBSET OF CHILDREN < 2 YEARS OF AGE:
(n= 11 available cases-see below)

- Two subjects could not be evaluated. One had a short period of study (4 weeks) complicated by infection; a second had insufficient data.
- Of the remaining 9 subjects , 6 responded to Epoetin with rise in hematocrit; five of the 6 responsive patients had reviewer-evaluated " good responses" defined as an increase in hct of at least 4 % and a response within 2-4 weeks after start of Epoetin; three patients did not respond.

Pt. Study arm	Age in years	Dose wk	Attain target	Incr. in hct -%	TX	AE	AE	Evaluation (by CBER reviewer) of hematocrit response
P	0.2	48	Y	*	0	hypertension	access complic.	Good response starting wk 2- 4
E	0.3	9	? N	none	0	Cardiac arrest-death	access complic.	No response
/E	0.4	36	Y	12 %	0	hypertension	access infection	Good response starting wk 2-4
/E	0.4	36	Y	9 %	wk 6	access complic.	-	Good response starting wk 2-4
/P	0.6	48	Y	8 %	wk 3, 5, 10	sepsis	hypocalc	Good response starting wk 2-4
/P	0.8	49	?	-1	*	hypercalcemia	-	No response
P	1.1	4	*	*	*	infection	-	*
P	1.4	24	N	-4	wk 24	infections	-	No response
E	1.5	36	Y	5 %	0	access complic	-	Good response starting wk 2-4
/P	1.8	26	Y	3 %	wk 14	hypercalcemia	-	Response starting wk 2-4
/P	2.0	13	*	*	*	*	*	*

In column 2 P refers to CONTROL arm subjects and E to EPOETIN arm subjects.
In column 4 dose wk refers to the numbers of weeks on study
Column 5-10 all refer to the doubleblind phase of the study
In column 5, Y indicates attainment of target hct and N failure to obtain target hct
Column 6 lists the increase in hematocrit between beginning and end of Double Blind phase; TX refers to # of transfusions of blood but not to the volume transfused. Volume information is available in study report
Columns 7 & 8 list only major AE .Column 9 is the reviewers judgment on the hematocrit response after examining appendix F.1 from Study Report of EPO 9002, volume 26, which provided patient by patient graphs of hct vs. time with additional AE and TX data
Hypocalc is hypocalcemia; hypercalc is hypercalcemia; complic is complications; TX is red cell transfusion
* insufficient absent data

10. REVIEWER ANALYSIS OF SUBSET OF PATIENTS WHO FAILED TO RESPOND TO EPOETIN

Two of 55 subjects in the EPOETIN arm and 7 of 50 subjects in the CONTROL arm 7/50 patients failed to attain the target hematocrit by the end of the Epoetin titration phase. The table below shows that the cumulative % of successful patients "flattens out" by week 9-10 of Epoetin titration. If instead of attainment of target hematocrit (increase hct by 6 or > % or hct in 30-36 range) a lower increment of hematocrit elevation is set as the target. the data suggest that almost all children will respond to Epoetin. Data from EPOETIN arm only, which were provided by sponsor, (Source -volume 6, appendix B.1.4,) showed that all pediatric subjectsraise their hematocrit 4% (54/54) and that 53/54 raised their hematocrit by 5% by end of double blind phase.The information suggests that there is a varied response to Epoetin, and that the non-responders may represent only occasional truly unresponsive children and more often slow responders or intercurrent clinical situations.

Week of Epoetin titration	Cumulative % of patients who attain target hematocrit (n= 105)
1	20.0
2	30.5
3	41.9
4	57.1
5	66.7
6	76.2
7	78.1
8	81.9
9	85.7
10	89.5
11	90.5
12	91.4 (n=96)

11 POST-MARKETING EXPERIENCE FOR PEDIATRIC CRF PATIENTS ON DIALYSIS (Source is volume 42, appendix 3-5).

Description: Forty-eight reports of post-marketing AE were provided by sponsor. Patients ranged from 0.5 to 18 years; 35/48 were CRF children on dialysis and the remainder had other diagnoses. Reports were collected from 6/1/89 to 11/30/95 (table below). Thrombocythemia is noted twice one of which was after high doses were given. There is an AE report (IND 4885/amendment 049 received 5/2/97) of thrombocytosis of 802,000 platelets/mm3 in a 52 year old who received 8 weeks of Epoetin. A possible drug reaction to cyclosporine is listed in three cases. Summary of literature review provided in section 3.5 failed to disclose any AE not included in Integrated Safety Report of clinical trials.

Reported toxicity	#	Narrative
Injection site pain	12	Symptoms assoc. with SC administration.
Impaired response to Epoetin	4	All 4 were associated with disorders which"predispose" to impaired response to EPO incl. hyperparathyr., peritonitis, renal transplant rejection, infection.
Drug interaction cyclosporine (CSA) (2 cases) Theophylline (1 case)	3	In case 1 the CSA level fell below therapeutic level 4 months after start Epoetin therapy; in case 2 CSA levels fell below therapeutic values before and after start Epoetin therapy. Both investigators felt that the CSA changes could be related to Epoetin. A 3rd case involved a premature infant who required multiple theophylline adjustments while receiving Epoetin.
Accidental excess dose	2	In case 1 a youngster inadvertently received 375 U/kg- Hgb rose to 10.5 g/dL 2 wks later; a second case was a child with a hct of 57 % after 13 doses of Epoetin (528 U/kg)- Epoetin discontinued and hct returned to 35%.
Neoplasm	1	Not believed related to Epoetin therapy
Weakness	1	Noted after 2 injections of Epoetin symptoms
Convulsions	7	Three cases had a prior history of convulsions. Convulsions reported 40-90 days after start Epoetin therapy. Hct values were 26 - 35% and in one case 20%. There was no hypertension, and 20% One of 3 died of a cardiac arrhythmia. In the remaining 4 cases the hct was 29-33% and patients were all hypertensive.Investigators suspected a relationship to Epoetin in 3 of 4 cases.
CVA	2	In the first case there was uncontrolled hypertension and siezures. A 16 year old treated with chemotherapy and on contraceptives had a cerebral thrombosis. Hct was 47% and the event was considered possibly related to Epoetin use.
Thombocythemia with leukocytosis and lymphocytosis	1	In case 1 a 23 month old with hemolytic uremic syndrome and glomerulonephritis developed all three symptoms 3 wks after Epoetin was increased from 300 to 450 U/kg weekly. Platelet count peaked at 974,000 /mm^3 and WBC and 36,900 /mm^3. Epoetin decreased.
Thombocythemia	1	A second case was in a 17 year old hospitalized for CHF and pulmonary edema who had a platelet count of 773,000 and WBC was 24,5000/ mm^3.
Hemolytic anemia	1	The third case was a child with systemic lupus erythematosus who developed hemolytic anemia 7 months after Epoetin therapy.
Alopecia	1	Patient with systemic lupus on Epoetin for 1 year- considered unlikely to be associated with Epoetin therapy.
Porphyria tarda	1	Considered to be possibly related to Epoetin therapy.
Urticaria & rash	1	Considered to be possibly related to Epoetin therapy
Temporary blindness	1	A 6 month infant with "prune belly " and history of nystagmus developed temporary blindness while on Epoetin at a hct of 28-31 %. Not considered related to Epoetin therapy.
Conjunctivitis	2	Not considered related to Epoetin therapy.
Hypertension	1	Immediately after administration BP rose from 150/110 to 210/165.
Hypotension	1	Hypotension immediately after receiving Epoetin.
Cardiac arrhythmia &hyperkalemia	1	Not considered related to Epoetin therapy
Thrombosis	2	In case 1 there was thrombosis of a cadavaric renal graft 24 hours after surgery-hct was 25%. In second case an adolescent with CRF secondary to cystinosis experience a renal transplant thrombosis
Leg pain at night	1	
Priapism	1	Seven weeks after starting Epoetin therapy.

PART IV- LITERATURE REVIEW

Published literature on use of Epoetin alfa in pediatric CRF patients on dialysis

- Sixty-one articles in English published between 1989 and 1995 were obtained by a sponsor using a computer literature search. Search terms were *erythropoietin and pediatric dialysis* and databases were Medline from 1966, Embase from 1974, Biosis Previews from 1970 and Science Citation Index from 1987. Sixty one reports were citedcontaining 864 subjects. The same patient could have been in more than one study. Both original articles and abstracts were included.Foreign language articles and reviews were excluded. Articles on erythropoietin beta were excluded. Articles which failed to address the indications in this application were excluded. Articles on studies sponsored by AMGEN and already in FDA files were excluded. (Source: Volume 3, section 3.5 & volume 42, appendix 3.6 A abstracts)
- CBER literature search using comparable search terms and citation sources produced 219 citations using the same search terms, *namely erythropoietin and pediatric dialysis*. The differences between the sponsor and CBER search was as follows; No articles were excluded from CBER search for lack of relevance; CBER search included a small number of foreign publications; Epoetin beta articles were not excluded; review articles were not excluded. In addition CBER search included literature up to the current time which was approximately 12 months later than the sponsor's search.The sponsor was asked to provide further details on those literature references they excluded in order to reconcile the findings. In an additional submission to the application (log number L97005974) the following information was provided on cited references excluded from the 61 references used to support licensure:
    - 67 were irrelevant to the proposed indication of increased hematocrit and lessened transfusions in CRF patients on dialysis
    - 39 were in a foreign language
    - 12 were review articles
    - 12 involved Epoetin beta
    - 10 were duplications of data
    - 5 relevant articles were omitted. These were provided and reviewed and , similar to the submitted data, support the use of Epoetin and provide some limited safety data.
    - 10 other miscellaneous articles are listed including some which were already sent to FDA as AMGEN sponsored studies.

  The sponsor's search includes 211 articles/abstracts and , considering the differences, was judged to be comparable to the CBER literature search.

Summary of 20 published studies provided by sponsor from literature review for dose and hematocrit response : Results are summarized for 20 articles in the table below (source- table 3.5.1, volume 3) selected for availability of outcome data. Starting pediatric doses ranged from 50-300 Units/kg/per week administered once, BIW or TIW. Time to hematocrit response was difficult to analyze because of wide differences in experimental design and because of failure to distinguish between time to minimum and maximum response and time to attainment of target level. All reports noted a response to Epoetin (increased hematocrit and/or decreased need for transfusions). Data on children who failed to respond were very limited (see reports in table below from Aufricht, Campos, Gagnadoux, Holloway); however the results available were consistent with the 91% response figure at 12 weeks reported in EPO-9002.

Data were reviewed for AE realted to Epoetin (see last column of table below).The most common complications were increased blood pressure, which in some cases required treatment and the need for iron therapy. One paper indicated that PD patients had" better" responses to Epoetin. A number of reports indicated improvement in exercise tolerance and QOL. Dabbegh and Fleischman, 1991, reported a significant increase in vascular access thrombosis from 0.08 to 0.15 per patient per month.

Transfusions: There were 14 published papers (153 subjects). All of the reports showed improvement in number of blood transfusions required.

Quality of Life (QOL): Twenty two published papers (361 subjects) reported improved quality of life or a measurement related to quality of life (Source is Volume 3, table 3.5.2). In 10/21 published papers positive effects included improved exercise tolerance, improved aerobic work capacity and effort tolerance along with feelings of well-being and improved stamina.

STUDY	Number in study	Fraction of children responding* to Epoetin and time of response in weeks	Mode of dialysis (HD or PD)	Adverse Events or other problems reported in study
Salley 92	8	Response started wk 6 and peaked wk 14-15	HD and PD	None
Sinae-Treiman 89	5	All started wk 3	PD	Increased hypert. in 3 subj.required dose adjustment of Epoetin
Warady 91	9	All started by week 7.9	PD	Increased treadmill time Pain at injection site
Aufricht 93	12	10/12 responded	PD	None
Campos 92	11	10/11 responded	HD	Increased hypert.in 2 subjectrs
Colan 91	10	No data	HD	Increase in exercise tolerance Rise in mean B.P. of 7% systolic and 17% diastolic
Dabbagh 92	34	No data - response by wk 8-14	PD and HD	Increased caloric intake Control of secondary hyperparathyroidism
Dabbegh & Fleischman 91	26	No data	PD and HD	Incidence access thrombosis incr. from 0.08 to 0.15/patient/month
Ellis 90	9	No data	HD	Epoetin more effective in PD than in HD
Fine 91	5	All responded	PD	Incr. B.P. 3 subjects
Gagnadoux 94	28	22/28 responded by wk 16.5	HD	Incr. B.P. in 43% of subjects
Goldraich 92	6	All responded by wk 12	PD	Pain at injection site Fe defic. in 2 subjects Rise B.P. in 1 subjects
Hisano 91	10	All responded by wk 24	PD	None
Holloway 91	34	32/34 responded by wk 24	PD	Need for Fe therapy
Lowrie 90	5	All responded	PD	None reported
Montini 90	10	No data	HD	Incr. heparin during dialysis Severe hypert. 1 subj. Transaminasemia in 2 subj. resolved by 3-8 weeks
Navarro 89	14	Response by wk 8-12	PD and HD	No data
Navarro 91	2	No data	HD and HD	No data
Offner 90	14	Response by week 4	PD	Hypertension in one subject
Ongkingco	7	Response by wk 7.6	PD	No data

* Responding- is defined as an increase in hematocrit to target level during the 12 week double blind phase Hypert. = hypertension or hypertensive episode: wk = week: HD= hemodialysis: PD = peritoneal dialysis. When available a range of times of response are given. Alternatively the landmark time at which a response success was judged to be present was provided.

5. **Iron deficiency and supplementation** : The literature review included 13 papers (130 patients) in which iron deficiency or need for supplementation was referred to. Ten/13 papers provided the specific number of patients (source- table 3.5.4 , see Enclosure 1). The papers emphasize the need to be aware of and to monitor iron status and provide oral iron when deficiency occurs in children.

6. ***General conclusions: The data provided from the literature search support efficacy for correction of anemia and reduction of transfusion requirements. With respect to safety the cited literature appears to involve similar problems to those encountered in adults, in particular elevation of blood pressure and need for monitoring for iron deficiency.***

B. Other published literature on the use of Epoetin alfa in pediatric CRF patients not on dialysis, zidovudine-treated HIV-infected pediatric patients and pediatric cancer patients on chemotherapy (Source: Volume 3, section 3.6 volume 3, section 9.0 references)

LITERATURE*	NUMBER STUDIES (# subjects)	LOCATION IN VOLUME 3
Pharmockinetic data on use of Epoetin alfa in children	6 (74)	TABLE 3.6.1
Use of Epoetin alfa in pre-dialysis pediatric CRF patients	17 (133)	TABLE 3.6.2
Use of Epoetin alfa in HIV infected pediatric patients with anemia after Ziduvidine treatment	3 (24)	TABLE 3.6.3
Use of Epoetin alfa in pediatric patients with anemia after receiving chemotherapy	7 (82)	TABLE 3.6.4
Total # references	42	

* Literature searches were from 1984-1995 and used either Medline alone or with Embase and Biosis

C. Literature on use Epoetin alfa in children with CRF not on dialysis: The 133 study patients in the 17 articles ranged in age from one month to 20 years and were treated for up to two years. Dose ranged from 50-300 Units/kg per week with most doses between 50-150 Units/kg/per week. In those reports which followed hematocrit response and transfusion requirements patients response times varied from 4 to 12 weeks.The major AE noted were hypertension (5 articles). Transient thrombocytosis , and flu-like syndrome were also mentioned.

D. Literature on use Epoetin alfa in HIV infection children with anemia secondary to Zidovudine.The 20 study patients in 3 articles, one of which is an abstract, ranged in age from 8 months to 17 years. Only 15 of the 20 children were clearly receiving Zidovudine ;

Mueller, et al- Eight patients were studied an average of 31.5 weeks. 7/8 had endogenous erythropoeitin levels below 500 units while one child had a high value of 3430 units. Most of the patients received > 4200 mg week of zidovudine.Epoetin dose varied from 150 to 400 Units/kg per week. In reviewing the report 3 or possibly 4 of patients had a clear response of increased hgb. The author stated that the use of Epoetin permitted the children to be maintained at the current high dose of zidovudine. The author reported that Epoetin was well tolerated ; very limited AE data was presented.

Robins, et al. - Five patients were studied for 8 weeks. Doses were 150 Units/kg/week. Endogenous Erythropoietin levels and Ziduvudine dose were not provided. It was reported that both mean hemoglobin and reticulocyte counts increased as compared to controls.

Zucotti, et al.-Eleven patients with a mean age of 4 years ,10 months, were given both G-CSF and Epoetin alfa 120 Units/kg/week given TIW/BIW for four months. There was no data provided on endogenous Erythropoietin levels and ziduvudine dose. The author reported an increase in hemoglobin and decrease in transfusions.

E. Literature on use Epoetin alfa in children with anemia associated with chemotherapy. In adults Epoetin is approved for use in non-myeloid tumors.In the seven studies on 64 children between 0.5 and 18 years of age doses between 50 and 400 Units/kg/per week were used. All of the reports noted increases in hemoglobin and hematocrit. No AE were reported.

PART V. POST-MARKETING SAFETY DATA

A. All ——— sponsored clinical trials were searched to identify pediatric patients (ages 0-16 years) treated with Epoetin alfa for anemia associated with CRF, HIV, infection and cancer. 21 pediatric patients were identified of whom 2 were treated for anemia of cancer, one for anemia associated with zidovudine treatment of HIV infection, 18 for anemia associated with CRF-dialysis. No pre-dialysis patients were found. (see CIOMS I forms- provided in Appendix 3.6C in volume 44.)

B. ——— worldwide AE postmarketing surveillance data base was searched for reports of children treated with Epoetin alfa under pre-dialysis , HIV or cancer indications.There were for six reports all for children under pre-dialysis. Three reports indicated children with hypertension with 2/3 having siezures, two children had skin reactions and the sixth had a fever. There were two reports of serious AE in children with cancer (gastrointestinal hemorrhage, septicemia and shock ; massive biiateral pneumonitis in the other). No reports were found in children with zidovudine related anemia.

C. AE reports for children treated for indications not approved in U.S. are found in appendix 3.6C in volume 44.

D. See III section 11.

PLA 97-0006

VI. CONCISE SUMMARY OF REVIEWER'S REPORT AND CRITICAL COMMENTS

PLA 97-0006 is a supplementary PLA to extend the current licensure of Epoetin alfa to the pediatric age group. The pediatric indications would include correction of anemia and reduction of transfusion requirements in; i) children with CRF on either peritoneal or hemodialysis; ii) children with CRF not on dialysis; iii) children receiving chemotherapy and iv) children receiving Zidovudine for HIV infection. The expanded license is supported by 4 Amgen-sponsored studies of 128 total patients from 0.2 to 19 years of age and by a literature review and by post-marketing reports. It would meet the requirements of revised Pediatric Rule (12/13/94) CFR201.57,f,(9), (iii) for CRF patients on dialysis and CFR201.57,f,(9)(iv)for indications ii, iii, and iv.

The major efficacy data which support the correction of anemia and decreased transfusions, and safety during initial therapeutic titration with Epoetin (12 week period) are found in study EPO-9002 (n=113). A subset of patients (n=74) who completed EPO-9002 were enrolled into study EPO-9118 of maintenance therapy with Epoetin alfa. Two small pilot studies, EPO-8702(n=10)and EPO 8905 (n=5), provide additional data.

1. EFFICACY

Study EPO-9002 adequately supports efficacy, that is the ability of Epoetin to increase hematocrit/hemoglobin and decrease or eliminate transfusions in anemic children- for the cited indications. *There were three critical, prospectively- declared primary endpoints in the CRF study. They were: (1) Comparative advantage of treated (referred to as EPOETIN arm) vs. placebo arm (referred to as CONTROL arm) patients in attaining "target " hematocrit during the double blind phase (first 12 weeks of study in both arms). 'Target" hematocrit was defined as reaching a hematocrit of 30% or > or an increase in hematocrit of 6% or greater above baseline. (2) Comparative advantage of Epoetin treated vs. placebo arm patients as demonstrated by a significantly higher mean hematocrit at end of double blind phase. (3) Comparative advantage of Epoetin treated vs. placebo arm patients in decreased number of transfusions /patient/four weeks.*

Study EPO-9002 had two arms to which patients were relatively equally and randomly allocated . The study was double blinded and placebo controlled in the first 12 weeks. The double blind phase permitted direct statistical comparison (for efficacy) of 55 Epoetin treated to 58 placebo-treated children . After week12 the CONTROL arm patients were started on a 12 week Epoetin titration course while the EPOETIN arm patients were placed on a maintenance, dose-adjusted schedule for 24 weeks. At week 24 the CONTROL arm finished Epoetin titration and started a course of 24 weeks of maintenance therapy. The non-concomitant research design (after week 12) facilitated collection of drug

activity and drug exposure data from all 113 patients both during titration and maintenance phases. In addition, it permitted confirmation of treatment effect by anticipating and testing for similar responses to Epoetin endpoints (although at different timepoints)in both arms. These latter comparisons were made after both arms received Epoetin titration doses (EPOETIN arm week 1-12, CONTROL arm week 12-24) and maintenance doses (EPOETIN arm week 12-36, CONTROL arm week 24-48).

Attainment of "target " hematocrit was the most central of the primary endpoints, since it was used to determine sample size prospectively. ——————————— One positive event (either rise of hematocrit to > 30% or 6% or > increase over baseline) at any time during the double blind period was scored as a success without confirmation. The result was that " success" could be and was triggered by random laboratory fluctuations in hematocrit values or by transfusions of blood. This proved a problem as evidenced by the incongruous finding that 58% of CONTROL arm patients attained the "target " hematocrit without treatment and despite the finding that the mean hematocrit of the CONTROL arm was unchanged after 12 weeks. Note the sponsor's protocol had prospectively hypothesized that 10% of the CONTROL arm would reach the "target " hematocrit. Nevertheless the difference between the Epoetin treated and the placebo-treated children after 12 weeks was still highly significant (EPOETIN arm 96% vs. CONTROL arm 58%, p=0.001).

More direct and convincing evidence for a treatment effect in these children is present in the change of mean hematocrit of +11.5% hematocrit units in the EPOETIN arm vs. +0.9 % in the CONTROL arm and in the decrease in mean number of transfusions / per patient/ 4 weeks of 0.23 in the EPOETIN arm vs. 0.12 in the CONTROL arm by the end double blind study phase. Statistical comparisons were significant for both endpoints.

Other findings and trends further support activity of Epoetin in children. There is a concomitant rise in hematocrit, in attainment of various target hematocrit/hemoglobin values by individual subjects, in the decrease in the amount of RBC transfusions, in transfusion independence in the Epoetin-treated vs. untreated subjects. Epoetin exposed subjects show a consistent and steady increase in hematocrit when individual patient results of time vs. hematocrit data are plotted; untreated children do not. An identical pattern of rise of hematocrit and decrease in transfusions is seen in the CONTROL subjects after delayed (non-concomitant research design) exposure to similar doses of Epoetin.

Initial doses of 150 Units/kg/week given TIW either subcutaneously (PD patients) or intravenously (HD patients) and a schedule for decreases but no increases in dose during the double blind phase (weeks 1-12) of study, and adjustments during the maintenance phase, appeared to provide satisfactory dosing information for labeling. The mean maintenance doses at end of study were 119, and 137 Units/kg/per week for EPOETIN and CONTROL arms respectively. The differences were not significant. PD and HD subsets show marked differences in maintenance dose (see discussion below).

2 SAFETY

The safety profile of the studied children was by and large similar to that observed to date in adults treated with Epoetin alfa- *with few exceptions. Integrated analyses of drug-exposed patients applied two analytic approaches. Subjects*

in the treatment and placebo arm of studies EPO-9002 (n=113) and EPO-8905(n=10) were compared for AEs during the 12 week double blind phase [double blind analysis] . Data was also collected on all patients for the entire period of drug exposure (n=119); there were 135.7 cumulative patient -years of drug exposure (all exposure analysis). Most data was expressed as % of affected subjects classified by AE Preferred Term/Body System and for events in Severe, Life Threatening, and Fatal , and Serious categories. AE which were of special concern because of a possible relationship to Epoetin therapy in adults (hypertension, convulsions, vascular access complications ,thrombotic events) were examined separately.

The double blind analysis comparison reported a higher incidence of myalgia (Preferred Term) and Skin and Appendage AE (Body System); the data were myalgia 20.3 and 6.3 % , and skin and appendages 23.7 and 9.4% incidence in treated and placebo arm subjects respectively. The skin and appendage AE were related to local reactions to injection of Epoetin . The myalgia was limited in duration and severity and rarely required treatment. Hypertension and convulsions and vascular access complications had a trend to higher values in the Epoetin treated comparative group; the differences were not significant and were consistent with adult studies which suggest that the above AE are low incidence events which could be related to Epoetin use but for which a clear etiologic or dose relationship and information on vulnerable populations is limited. Only one death occurred during the trial in the EPOETIN arm and it did not appear related to the study drug. The one withdrawal from study due to intolerable AE was in the CONTROL arm.

3. The data indicate that the effect of Epoetin treatment may be different in PD as opposed to HD children-with CRF. *Results show that PD patients respond faster to similar doses of Epoetin during the initial titration of patients into the target range. In addition PD patients require a lower maintenance dose of Epoetin [PD patients 97 Units/kg/week; HD 145 Units/kg/week). On the other hand the dose of Epoetin needed to attain the target hematocrit and the eventual height of hematocrit attained is not clearly different between HD and PD children .*

The direct data show substantial differences (see Reviewer Report, IIa, section 5; CBER Statistical Report on time to event analysis comparing HD and PD groups; Sponsor's data in SOE). In addition there is indirect /inferential support for the PD-HD differences. Perusal of rate of response of individual patient plots of time vs. hematocrit shows discernible differences between PD and HD children. The rate of RBC transfusions/patient during the double blind phase was lower in PD patients (in EPOETIN arm 3.0 HD vs. 0 PD; in CONTROL arm 4.1 HD vs. 2.8 PD).The difference observed in maintenance dose of Epoetin in study EPO-9002 (an Epoetin titration phase of 12 weeks followed by 24 week maintenance phase) was even more marked in study EPO-9118 which followed these same patients on further maintenance Epoetin for an average of 36.9 more weeks. If the PD- HD difference in maintenance dose reflected a lack of equilibrium of one mode of dialysis subset on maintenance therapy, it should diminish with time. There is at least one literature report of PD-HD difference (Mueller-Weifel, D.E. etal .Contrib. Nephrol. 1988,66:71-84).

A CBER

analysis which used a "confirmed" 6% increase in hematocrit and a time to event analysis found the same favorable response to Epoetin as did the sponsor using the prospectively defined " attainment of target hct'.

Explanations for the PD-HD differences encountered range from the possibility that PD children receiving SC Epoetin and HD children receiving IV Epoetin represent different stages of disease or disease populations or that the pharmacokinetics of SC and IV administration of Epoetin are different . Explanations on a cellularlevel would involve Erythropoeitin receptors or cell sensitivity to the agent.

4. The higher incidence of myalgia in Epoetin treated children is of unclear origin. The majority of clinical reports describe short term muscle cramps. There is a disproportionately higher number of HD than PD patients.

5. There is very little information on children under 2 years of age and more critically under 6 months treated with Epoetin. The summary of the 11 children < 2 years in part III, section 9, suggests that even young children do respond to Epoetin. Furtherinformation on Epoetin treatment of premature children is being obtained and may provide reassurance.

6. It is difficult to determine with any exactitude how many children fail to respond to Epoetin since there is wide latitude in the dose needed and time to response, a number of clinical states are reported to transiently interfere with response, and transfusion was permitted at discretion of the investigator during the study making rate determinations difficult. (see part III, section 10). It is concluded that most children respond to Epoetin and that the pediatric data are consistent with 95% responder rate referred to for adult populations.

7. The indications for other than CRF children on dialysis are supported by literature reviews. These reports suggest that Epoetin has a similar effect/activity to that seen in CRF children on dialysis in raising the hematocrit/hemoglobin and decreasing transfusion requirements .

1. *IT IS RECOMMENDED THAT EPOETIN ALFA LICENSURE BE EXTENDED TO PEDIATRIC USE FOR THE CITED INDICATIONS.*
2. *THE CHANGES IN LABELING SHOULD NOTE THE DIFFERENCES IN PD VS. HD RESPONSIVITY AND THE LIMITED DATA AVAILABLE ON VERY YOUNG CHILDREN.*
3. *FOR OTHER THAN CRF CHILDREN ON DIALYSIS THE LIMITATIONS PROVIDED FOR IN THE PACKAGE INSERT BASED ON ADULT DATA SHOULD BE MAINTAINED.*

6/9/97

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